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April 14, 1999

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: FDA Docket No. 98D-0785; Draft Guidance For Industry: Developing Medical Imaging Drugs and Biologics

Dear Sir Madam:

These comments on the Food and Drug Administration's (FDA's) October 1998 "Draft Guidance for Industry: Developing Medical Imaging Drugs and Biologics" (Draft Guidance) are submitted by Bracco Diagnostics Inc. (BDI).

BDI would like to commend FDA on its efforts to establish a guidance for medical imaging drug products, and is delighted to participate in the development of Agency policy in this area. We, as BDI representatives, participated in FDA's public meeting on the Draft Guidance that was held on March 26, 1999. We have also contributed to the Council on Radionuclides and Radiopharmaceuticals (CORAR) and Medical Imaging Contrast Agent Association (MICAA) documents that the Agency will receive directly from those organizations. We are submitting additional comments to reemphasize and expand upon the issues that were discussed at the public meeting. At the March 26th public meeting FDA officials indicated that significant changes are likely to be made to the guidance as a result of public feedback. We request that FDA propose these changes in a new draft for further, abbreviated public comment before issuing a final guidance.

I. NON CLINICAL PHARMACOLOGY/TOXICOLOGY

A. Entry and Residence in Group 1

It is proposed in the Guidance document that the non-clinical dose from which the margin of safety for the clinical dose is calculated should be the No Observed Effect Level (NOEL).

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However, it is the NOAEL (No Observed Adverse Effect Level) that is currently used in the therapeutic field for determination of safe dose for humans. The NOAEL is the highest dose level that does not produce a significantly elevated increase in an adverse response (Casarett & Doull's Toxicology; Page 80, 1996; 5th Edition, McGraw-Hill Publishers). Exaggerated pharmacologic effects such as dryness of mouth, taste perversion after administration of a metal binding compound, change in the production of body fluids such as saliva or tears, and drowsiness as well as pain at the site of injection are not regarded as safety issues.

Exaggerated pharmacologic effects (expected observable effects that do not represent a high or unknown risk) should not be used to set the clinical dose ratio to minimal toxic dose threshold and, therefore, membership to group 1. An accepted norm for the relationship between the NOAEL and the upper bound for the initial clinical dose for a phase I clinical trial of a THERAPEUTIC drug is explained in the following article (Enclosure #1):

Considerations for Toxicology Studies of Respiratory Drug Products: J.J. DeGeorge, C.H. Ahn, P.A. Andrews, M.E. Brower, Y.S. Choi, M.Y. Chun, T. Du, D.Y. Lee-Ham, W.D. McGuinn, L. Pei, L.F. Sancilio, W. Schmidt, H.V. Sheevers, J.J. Sun, S. Tripathi, W.M. Vogel, V. Whitehurst, S. Williams, A.S. Taylor. Regulatory Toxicology and Pharmacology, 25, 189-193, (1997)

The following excerpts are taken from the above article:

a) The upper bound for the initial dose for a Phase I clinical trial is generally a fraction of the no-observed-adverse-effect-level (NOAEL) in animals. Traditionally, this fraction has been calculated to be less than 1/10 the NOAEL in rats or 1/6 the NOAEL in dogs.

b) Generally, a smaller safety factor is appropriate for comparisons based on body surface area.

c) When animal toxicity is reversible and readily monitored in humans, escalation to doses above the animal NOAEL may be acceptable.

Our extensive experience with radiopharmaceuticals has shown that little or no biological response in animals is detected at doses up to about 50-100 times the human dose. We believe that to be included in Group 1, the NOAEL, as adequately adjusted in the most appropriate animal species, should be at least 5 times (see Enclosure #2 for information on safety factors) the maximal dose to be used in the initial human study.

If there are no significant adverse events (as described in ICH Medical Dictionary for Regulatory Activities commonly referred as MedDRA) in the clinical trials, doses up to the NOAEL (based on the most appropriate species) could be given.

If the repeat dose animal toxicity studies are needed for the NDA, these should be done after phase I and II clinical studies are completed and the "proof of concept" is fully established.

Certain ultrasound contrast agents (UCA), such as intravenously administered microbubbles, microaerosomes and related microparticles may qualify for Group 1 status similar to Group 1 diagnostic radiopharmaceuticals. These diagnostic UCAs are administered in low mass (e.g., 0.2 - 2.0 mg per examination; about 0.003 to 0.03 mg/kg, based on 70 kg individual) as single or limited repeat doses and eliminated rapidly due to short biological half-life. Therefore, UCAs should be considered for Group 1 status.

B. Absorption, Distribution, Metabolism, and Excretion

We believe that pharmacokinetic studies in animals are not necessary for Group 1 compounds (diagnostic radiopharmaceuticals as well as UCA) that are administered to clinical subjects as "single dose."

As indicated in DeGeorge, et al., 1997 (Regulatory Toxicology and Pharmacology, 25, 189-193; See Enclosure 1), PK data are used in the therapeutic field to:

a) Set the upper limit for clinical dose escalation studies.
b) Set the amount of escalation between doses.
c) Set the margin of safety for irreversible toxicities or toxicities that are difficult to monitor clinically.
d) When making comparisons between preclinical and clinical exposures in relation to toxic endpoints.

The above publication states, "Without PK information, it is generally preferable to use dose comparisons based on body surface area rather than body weight."

In another publication (Enclosure 3; DeGeorge et al., Cancer Chemother. Pharmacol., 41, 173-185, 1998), it is stated that:

"While not essential, information on the pharmacodynamics and pharmacokinetics of drugs is extremely valuable for supporting the safety profile"

"although not required, pharmacodynamic and pharmacokinetic studies can provide substantial additional support for the safety profile (starting dose, escalation)."

Since Group 1 compounds are characterized by low mass and rapid elimination and are administered as "single dose," radiation dosimetry data from animal study should be sufficient to determine 'fate' of the drug over time. In addition, AUC, biological half-life, etc. can be estimated from the distribution of radioactivity in various tissues of the body over time using classical mathematical PK methods.

C. Safety Pharmacology Studies

Toxicity study in rodents should be designed to address Safety pharmacology issues. No separate safety pharmacology studies should be necessary for Group 1 compounds.

D. Special Toxicity Studies

Animal toxicity study(ies) should be designed to include 'local tolerance' of an intravenously administered diagnostic agent. Separate animal study to address local tolerance need not be necessary.

E. Bridging studies to address formulation changes

Issues pertaining to reformulations (e.g., safety of new excipient) are not addressed in the document. A single dose toxicity study in an animal species that can address safety of new excipient(s) alone or in combination with active and/or inactive ingredients within the new formulation is generally sufficient.

F. Radiation Dosimetry

It should not be necessary to use both MIRD and ICRP methods to assess radiation safety. Either MIRD or ICRP should be adequate.

II. Medical Imaging Drugs As Distinct From Therapeutic Pharmaceuticals

In many respects, FDA's approach to safety and efficacy demonstrations for medical imaging drug products closely parallels its approach to the establishment of safety and efficacy for therapeutic drugs.[1] A critical point that we wish to emphasize, and that underlies many of the specific issues discussed below, is that the physical and chemical properties of medical imaging drug products, as well as the significance of those properties, are distinctly different from those of therapeutic pharmaceuticals. For medical imaging drugs, physics and physical chemistry are as important (if not more important) than biology and biochemistry. Unlike therapeutic drug products, the clinical usefulness of a medical imaging drug is not directly related to the drug's *in vivo* effects.

In addition, the manner in which physicians use medical imaging drug products, and the benefits that medical imaging drugs afford to patients, are quite different from how physicians use, and patients benefit from, therapeutic drugs. Certain medical imaging drugs (e.g.,

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1 See, e.g., Draft Guidance at 17-19, 21, 23, 25, 36.

radiopharmaceuticals and stabilized microbubbles) are typically administered in small mass doses for single or limited repeat use, and they are rapidly eliminated from the body.

TABLE 1. Comparative Mass Dose Ranges

Modality	Component	Amount (Single Use)
Nuclear	^{99m}Tc complex Ligand, carrier	1 – 10 ng 0.01 – 10 mg
Ultrasound	Gas Shell material	0.2 – 2.0 mg 0.5 – 10 mg
MRI	Gd^{+3}- complex Ligand	2 – 12 gm 0.01 – 0.50 gm
X-ray	Iodinated moiety Excipients 0.05% Impurity	15 – 150 gm 1.5 – 100 mg 7.5 – 75 mg

TABLE 2. Comparative Elimination

Modality	Component	Elimination
Nuclear	^{99m}Tc complex	100% $t_{1/2}$ = 361.2 min
Ultrasound	Gas	96 +/- 23% $t_{1/2}$ = 1.3 +/- 0.7 min
MRI	Gd^{+3}- complex	95 +/- 5% $t_{1/2}$ = 96 +/- 6 min
X-ray	Iodinated moiety	97 +/- 2% $t_{1/2}$ = 123 +/- 8 min

Given these distinctions, we believe that it is inappropriate to apply to medical imaging drugs the same or similar measures of safety and efficacy as are typically applied to therapeutic pharmaceuticals.

III. General Considerations For Safety Assessments of Medical Imaging Drugs

The Draft Guidance indicates that there may be special characteristics of medical imaging drugs that could allow nonclinical and clinical safety assessments to be "relatively efficient" or "tailored." These special characteristics include dose, mass, route of administration, frequency of use, and biological, physical, and effective half-lives.[2] The Draft Guidance also states that Group 1 designation may be based on a history of sufficient clinical use or previous clinical trial experience demonstrating no clinically detectable allergic, immunologic, biochemical, physiologic, or pharmacologic responses, and no dose-related toxicological risk or adverse event profile, at clinical doses or dosages.[3]

In some cases, sponsors of contrast agents develop an approved agent for an alternate route of administration. For example, a Gd^{+3} chelate approved for intravenous use in MR imaging might be developed for alternate routes of administration (oral, rectal, intraarticular, etc.).[4] Under the Draft Guidance, it would appear that the history of intravenous use could qualify the agent for Group 1 designation. Moreover, if it has been shown that there is virtually no systemic absorption via these alternate routes, it would appear that this information, in conjunction with the safety profile of intravenous use, would constitute a sufficient safety evaluation. We request clarification on the role that route of administration and lack of systemic absorption might play in "tailoring" the nonclinical and clinical safety assessment in these circumstances.

IV. Establishing Claims For Medical Imaging Agents

The Draft Guidance states: "To establish a claim for a medical imaging drug, a sponsor or applicant should characterize the drug's clinical usefulness and demonstrate that the information provided is valid and reliable. Clinical studies should be performed in defined clinical settings." It is unclear whether different defined clinical settings are intended to mean different patient populations. If this indeed the case, then it might be necessary to conduct separate clinical trials in each of these patient populations. We are concerned that we will have to enroll larger and larger numbers of patients with finer and finer designations of disease which will require greater expense and lengthy clinical trials.

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2 Draft Guidance at 15, 34.

3 Id. at 35.

4 Approval under an abbreviated NDA may not be possible for such an agent where a new indication is sought.

V. General Considerations in the Clinical Evaluation of Medical Imaging Drugs

(Also, see comments above, Section I. Non-clinical Pharmacology and Toxicology, B. Absorption, Distribution, Metabolism, Excretion)

The Draft Guidance states: "Pharmacokinetic evaluations should address the absorption, distribution, metabolism, and excretion of all components of the drug formulation and any metabolites." This requirement is unduly burdensome for medical imaging drugs. PK evaluations for therapeutic pharmaceuticals are typically performed only on the active component. Other components may be evaluated in case of *in vivo* activation, as for pro-drugs, or in case of specific metabolites having pharmacologic activity. Most medical imaging drugs are pharmacologically inert and are excreted unchanged. Finally, certain medical imaging drugs, such as air based ultrasound contrast agents, utilize an active component for which PK evaluations may only be performed using radiolabeled techniques. Similarly, PK evaluations of other components of a drug product that are integrated into biological pools, such as lipids or amino acids, may require radiolabeled studies. These studies can be extremely difficult, expensive and time consuming to perform. Also, they may not be considered to be ethical by Institutional Review Boards.

VI. Special Considerations in the Clinical Evaluation of Efficacy

The Draft Guidance notes that "In studies that are intended to demonstrate efficacy of a medical imaging drug, evaluations of images should be performed by readers that are both independent and blinded . . . ."[5] We appreciate the importance of eliminating bias from the efficacy evaluation. However, we disagree with, and request that FDA reevaluate, certain of the reader characteristics and blinding criteria proposed in the Draft Guidance.

A. Image Evaluations – Characteristics of Readers – Independent Readers

According to the Draft Guidance, "independence" means that a reader cannot have participated in Phase 3 studies, and cannot be affiliated with the sponsor or with institutions where the studies were conducted.[6] We submit that the requirement that a reader not be affiliated with an institution where the study was conducted is too onerous. It is often difficult to find readers with enough experience and expertise to evaluate new agents, especially in large trials. We suggest that FDA allow blinded readers to come from the same institution as an investigator if they are not involved in the study. FDA should also allow investigators to read images that are obtained from study sites other than their own. Such modifications to the independence requirement would facilitate selection of appropriate readers without introducing undue bias into the efficacy evaluation.

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[5] Draft Guidance at 25 (emphasis in original).

[6] Id.

B. Image Evaluations – Characteristics of Readers – Blinded Readers

As defined in the Draft Guidance, "blinded" means that the reader must be unaware of the treatment/agent that was used to obtain an image, and must have limited or no knowledge of patient-specific clinical information and the study protocol.[7] We urge FDA not to insist that fully blinded readings be the only acceptable way to measure efficacy of medical imaging drugs. Although these readings may reduce bias in a statistical sense, they often produce a highly inaccurate measure of the effectiveness of the agent as it will perform in defined clinical settings. This is because the fully blinded reader is not familiar with the agent and the imaging technique practiced, and lacks basic information on the anatomy, positioning, and condition of the patient that may be essential to rendering a reliable and valid interpretation. As a result, the data generated by such readings have limited utility to clinicians as well as third party payers. We believe that physicians are entitled to information that will enable them to evaluate, and make appropriate clinical use of, medical imaging products. This requires that a product be tested under conditions that are consistent with the manner in which the physician will use the drug, and that the results of such testing be conveyed to the physician in product labeling.

At the March 26th meeting, FDA indicated that the Agency has rethought the requirement that efficacy be based solely on studies in which readers receive little or no information about the patient or the study protocol. Dr. Mills described a sequential unblinding methodology, modeled after a medical imaging grand rounds, in which images would first be presented to a reader with "full blinding," and then with complete clinical information and all supporting imaging studies (as prospectively designated in the protocol), but no outcome.

Although we support FDA's departure from strict reliance on full blinding as the basis for efficacy evaluation, we disagree with the sequential unblinding model as applied to most contrast agents. The sequential unblinding model --- could result in the generation of at least seven data sets: the pre-contrast alone, post-contrast alone, and paired readings in step one (fully blinded) independent readings; the same three types of readings in step two (informed) readings; and the on-site investigator readings. The multiplicity of data sets could introduce confusion into the review process, with likely disagreement between the sponsor and FDA on the relative weights to be accorded to each data set. Moreover, the sheer number of readings would – in addition to significantly increasing the costs of studies – pose problems for recruitment of competent readers and the establishment of reading schedules that avoid reader fatigue, especially in large trials.

We believe that fully blinded readings may be appropriate in certain cases. For instance, if the unenhanced images have sufficient anatomic detail to provide a medical context for accurate interpretation (e.g., chest x-ray, certain CTs and MRIs), then fully blinded readings could yield useful results. Also, if the imaging modality and technique(s) are highly reproducible and have low interexamination variability (i.e., from patient to patient, instrument to instrument,

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[7] Id.

physician to physician, technologist to technologist), then fully blinded readings may be appropriate. Finally, if the clinical usefulness of the drug is primarily based upon technical endpoints, then fully blinded readings could be appropriate.

However, for most contrast agents, the effectiveness evaluation should be based on selectively informed readings in which readers are provided with the following information:

a) Prospectively defined demographic information (e.g., age and sex)
b) Physical examination results as appropriate
c) Results of medical diagnostic tests other than similar imaging tests
d) Essential information on the imaging technique
e) Anatomical region of interest, if not clearly obvious (especially for ultrasound and nuclear agents)

Readers in such studies should not be provided with the following information:

a) Identity of the treatment
b) Information on the imaging protocol
c) Dose
d) Method of administration
e) Inclusion/exclusion criteria
f) Final diagnoses, truth

In closing, let us once more express our gratitude to FDA for having arranged the meeting of March 26th. We appreciate the many demands placed on FDA staff's time and that special efforts were made to participate in the meeting. The active participation by FDA staff resulted in a productive dialogue that clarified many concerns.

Thank you for considering our request.

Sincerely,

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RE: **Draft "Guidance For Industry: Developing Medical Imaging Drugs and Biologics" (Docket No. 98D-0785)**

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